Fibrin Gel Architecture Influences Endogenous Fibrinolysis and May Promote Coronary Artery Disease

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A
n altered fibrin network architecture has been associated with premature coronary artery disease (CAD). Hypofibrinolysis, ie, impaired dissolution of fibrin in blood clots, is another common finding in such patients. Hypofibrinolysis is associated with elevated activity of inhibitors of the fibrinolytic process, particularly of plasminogen activator inhibitor-1 (PAI-1) and thrombin activatable fibrinolysis inhibitor (TAFI), but it is also influenced by the characteristics of the fibrin network itself. However, previous studies on fibrin architecture, its regulation, and implications for CAD have been hampered by imperfect and/or incomplete methodology. Thus, the relationships between fibrin structure, fibrinolytic function, and premature CAD warrant further thorough examination. This issue of *Arteriosclerosis, Thrombosis, and Vascular Biology* features a comprehensive investigation of physical and viscoelastic characteristics of fibrin clots formed ex vivo from plasma samples, their relationships to fibrinolysis rate, and potential role in CAD.

See page 2567

Both the morphology and mechanical properties of fibrin influence susceptibility to fibrinolysis. Fibrin structure is generally assessed by using liquid permeation, light scattering, scanning electron microscopy, and confocal microscopy, from which variables such as the fiber thickness, length and density, and the number of branch points and porosity of the network are derived. Blunted fibrinolysis is associated with a tight fibrin structure composed of thin and short fibers with increased number of branch points, and small pores. Individual thick fibers are actually lysed at a slower rate, but tight network configurations display a significantly higher fiber density compared with loose structures, which renders them more difficult to be lysed because there are more fibers to be processed and increased restriction to the permeation of fibrinolytic factors through the network.

The mechanical properties of fibrin can be quantified by determining the response to forces to which fibers are subjected. Either static or dynamic measurements can be made, oscillatory motion being an example of the latter. Recording of the oscillations of a torsion pendulum attached to a sample (clot) on careful application of shear forces allows calculations of the storage modulus, which reflects the stiffness or resistance of the clot to deformation. In general, clots with increased stiffness are digested more slowly by plasmin than less stiff clots. This was clearly shown in experiments in which the stiffness of the clot and its resistance to fibrinolysis increased in parallel on addition of factor XIII, whereas inhibitors of the factor XIII–catalyzed reactions greatly reduced both clot stiffness and lytic resistance. Also, fibrin formed with a recombinant fibrinogen truncated at Aα chain residue 251 was less stiff and digested faster in plasmin-catalyzed experiments than control fibrin formed with recombinant fibrinogen with common Aα chains containing 610 amino acid residues, although the fibrin formed from the truncated fibrinogen was composed of thinner and denser fibers, with more branch points, than the control fibrin. Regarding mechanisms, little is known about the relationships between fibrin’s mechanical properties and rate of fibrinolysis.

Genetic and environmental factors determining fibrin structure have been extensively studied in recent years (detailed reviews in references). In brief, fibrin with a tight network conformation is observed under circumstances with increased plasma fibrinogen concentration (genetically determined or raised in association with age, female gender, infection, inflammation, hypertension, diabetes and hyperlipidemia), as well as in the presence of increased thrombin (or prothrombin) concentration. Also, increased availability of modifiers (such as homocysteine or lipoprotein (a)) seems to contribute to a tighter fibrin structure as do certain proteins that cross-link to the fibrin network. In addition, qualitative modifications of the fibrinogen molecules originating from nonsynonymous genetic variation, alternative splicing, post-translational modifications, and proteolytic degradation have also been observed to influence fibrin morphology. Determinants of the viscoelastic properties of fibrin, on the other hand, have been less studied. However, crosslinking (or ligation) of fibrin seems to be an established important factor. First, 5-fold increase in fibrin stiffness was observed when fibrin crosslinking was induced with factor XIII and normalization was achieved when factor XIII was inhibited. Second, decreased stiffness was observed in fibrin formed with recombinant fibrinogen truncated at Aα chain residue 251 that is associated with reduced crosslinking by factor XIII, compared with control fibrin. And third, fibrin gels formed with the recombinant fibrinogen γ’ variant were 3-fold stiffer than fibrin formed with the common γA variant, most likely because of greater crosslinking. The γ’ variant, which arises from alternative processing of the fibrinogen γ chain mRNA, serves as a carrier of factor XIII.


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The current knowledge of fibrin gel structure (morphology and mechanical properties), its influence on the rate of fibrinolysis, and the overall role of hypofibrinolysis in CAD has been generated through the work of many research groups in the past 40 to 50 years. The article by Dr Collet et al appearing in this issue of ATVB ties current concepts nicely together in one single study and provides exciting novel information. The authors studied the morphological and viscoelastic properties of fibrin formed ex vivo from plasma samples of patients with premature CAD by using confocal microscopy and a torsion pendulum, and examined the fibrinolysis rate by continuous monitoring of the viscoelastic properties after addition of tissue plasminogen activator. The fibrin formed from the patient plasmas was observed to be stiffer and composed of thinner and shorter fibers which were arranged in a denser and less porous network that lysed slower compared with fibrin networks formed from control plasmas. The stiffness and length of the fibers, and to a lesser extent the plasma PAI-1 concentration and gender, were found to be independent determinants of the fibrinolysis rate in multivariate statistical analysis. Most remarkable was the observation that fibrin stiffness was the sole independent correlate for premature CAD among a set of variables that included parameters of fibrin morphology and mechanics along with an array of established hemostatic, inflammatory, and metabolic risk indicators. This interesting novel finding suggests that some physical properties of fibrin may have a unique role in CAD and potentially constitute a link between impaired fibrinolytic function and increased risk of CAD. Indeed, a further corollary of this observation is that fibrin structure is likely to be a major regulator of (endogenous) fibrinolysis. In this respect, fibrin stiffness may be considered a sensitive measure of the contribution of many (hemostatic) factors which, by giving strength and resistance to the clot, favor the occurrence of thrombosis. The loose ends left in the work by Dr Collet et al include the identity of the factors that determine fibrin stiffness, which are not even touched on. One would for example have liked to learn more about the potential roles of factor XIII activity and fibrinogen γ concentration, including any effects of genetic variants that may, in turn, influence these potentially relevant actors. Needless to say, the relationships of fibrin stiffness to CAD also need to be demonstrated in a prospective study, circumventing the multiple confounders inherent in a small-scale retrospective case–control study.

A better knowledge of the determinants of fibrin clot structure and thrombus susceptibility to lysis may have important implications for thrombolytic therapy. If fibrin stiffness proves to be a strong determinant of the fibrinolysis rate and an important risk factor for atherothrombotic diseases in future studies, it should be studied in greater detail to construct a platform from which rational approaches aiming at reducing stiffness and the ensuing lytic resistance of thrombi can be launched.

Disclosures

None.

References

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